EHC NOW!

EHC Compilation Newsletter

January-April 2018

EHC Newsletter January-April 2018

Table of Contents

The EHC would like to acknowledge its 2018 Corporate Sponsors:

- Platinum Sponsor: Bayer, Biomarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire and Sobi
- Silver Sponsor: Alnylam, Biotest, Kedrion, Sanofi Genzyme and UniQure

Editor: Amanda Bok
Editorial Committee: Radoslaw Kaczmarek, Raia Mihaylova, Olivia Romero-Lux, Laura Savini (currently on maternity leave)
AISBL EHC registered office: rue de l'Industrie 10, 1000 Brussels, Belgium
Tel. +32-2-893-24-70 - Email office@ehc.eu - No. 887.106.966

President and CEO Report

Change. This is the 'movement' that is currently reverberating in the rare bleeding disorders community and in turn has reflected back on the European Haemophilia Consortium (EHC). From the emergence of novel therapies to the changing haemophilia landscape, the needs of our national member organisations (NMOs) are shifting and we are adapting accordingly.

Brian O'Mahony
EHC President

Amanda Bok
EHC CEO

That being said, we would first like to welcome you to the new format of the EHC Newsletter! As you know, we have produced newsletters that offer up-to-date information three times a year on EHC activities, National Member Organisation (NMO) news and the latest scientific and medical developments in the field of haemophilia and other congenital bleeding disorders. It is a mouthful to say and with over 60 pages per issue it was, as a result, a handful to read. Moving away from the length but sticking to the coverage, we are now publishing content on a weekly basis. More dynamic and engaging, we are excited to bring you 'EHC NOW!' every Wednesday in the format of videos, articles and live interviews. For those of you who like the old newsletter, we will still be compiling all the materials on a quarterly basis and sending it out in its written format. **EHC NOW! materials are posted both on our website and social media.*

New Products Newsletter

With change often comes uncertainty of the unknown. Though novel therapies bring much awaited hope and excitement, they also carry a number of questions for both patients and health care professionals. Furthermore, with the rising number of treatment choices available and more in the pipeline, it is difficult to follow the different updates, statuses and advantages of each. To guide our NMOs, we have committed to producing a 'New Products' newsletter, the first issue of which will be sent out later this month.

EAHAD travel grants

We pitched the idea earlier that it would be great to make travel and participation possible for some of our patient representatives at the Congress of the European Association for Haemophilia and Allied Disorders (EAHAD). We are delighted to have received funding to be able to offer EAHAD travel grants and we have six patient representatives from our community that were awarded these grants. Hopefully this will be a yearly thing! Stay tuned for reports from this years' grant recipients on how they found the experience and what information stood out to them from the EAHAD 2018 Congress.

EHC Strategic Plan 2018-2022

We launched, for the first time ever, an independent third-party external stakeholder consultation process last year, which we wrapped up in December 2017. We had consulted all of our NMOs, as well as a number of important and broad stakeholders including industry, health care providers, regulators, other patient organisations and a number of other partners on their vision for the future of the EHC. We went through all of that rich feedback at our strategic retreat in January 2018 so hopefully we will soon have the language for our new strategic plan 2018-2022.

Updated Council of Europe Resolution on haemophilia therapies / EHC advocacy video

The end of 2017 set us up for a strong start in 2018. We were very excited to see the Committee of Ministers of the Council of Europe issue a new Resolution on haemophilia therapies, which combines their last Resolution with the latest set of haemophilia recommendations into one. We feel like that makes a really great advocacy tool for our national members to advocate nationally for better access to treatment and care. To put a face to the challenges that are advocated for, the EHC has further produced an advocacy video that highlights the difference in patient quality of life based on whether these recommendations are implemented by European governments or not. You can view the video, and use for advocacy purposes, here.

Memorandum of Understanding with the European Association for the Study of the Liver (EASL) Foundation to eradicate hepatitis C from the haemophilia community by 2022

Last year we also agreed to sign a Memorandum of Understanding with the EASL Foundation and agreed on a joint strategy on eradicating HCV from the European haemophilia community by 2022.

Finally, in the time since our last EHC newsletter, our colleague Kristine Jansone, Inhibitor Program Officer, gave birth to a beautiful baby boy whose addition to our community we are delighted to announce!

Comprehensive Care in Haemophilia: Comprehensive Care through the Prism of the European Principles of Haemophilia Care

Interview with Professor Brian Colvin, lead author of the European Principles of Haemophilia Care; Interview by Raia Mihaylova, EHC Communications Officer

2018 marks ten years since the publication of the European Principles of Haemophilia Care, which set the standard for the provision of comprehensive haemophilia care in Europe. Established with the idea to bring haemophilia treatment and care to an adequate level throughout the continent, the Principles have also been used as an important tool to both assess and advocate for improvements in countries where optimal standards are lacking. On the tenth anniversary, we talk to lead author Professor Brian Colvin and revisit these fundamental principles and the haemophilia landscape they were written in.

RM: What does comprehensive care mean in relation to haemophilia?

BC: *"Comprehensive Care" really means looking after all the needs of a person with haemophilia. The list of potential services is very long but it includes all physical, social, psychological and emotional needs of the person and of their family.*

Professor Brian Colvin

People with haemophilia see their haemophilia centre as the complete source of all the things that they need and that is what we try to deliver. This requires the engagement of many groups, including governments and patients. There is a danger that if the haemophilia centre doesn't offer all the necessary services, physicians or surgeons who are not familiar with haemophilia will make inappropriate decisions. For instance, in the UK it may be difficult to get good dental care, specifically for people with haemophilia. It is very important that excellent dental care is available for young children with haemophilia and the parents need to have it really emphasized, that this dental care is critical and that it should be provided by the centre, rather than them just by going on to a general dentist.

RM: I like that you mentioned the involvement of governments and patients in the comprehensive care as well…

BC: *The crucial importance of the involvement of government and partnership in care has been a key part of the work we have been doing together. I think that if you look at comprehensive care at its widest scale, then all its stakeholders must be involved.*

RM: How do the European Principles of Haemophilia Care capture the concept of comprehensive care and why were those exact ten Principles chosen?

BC: First of all, the idea was to cover the whole of comprehensive care, not just the comprehensive care centre. And you'll see in the Principles that they cover organisation, governments, bureaucracy, funding, delivery and all the detail of what is required to look after somebody with haemophilia. For their establishment, it had to be a partnership, it had to be teamwork and that is why we wanted to make sure that all the stakeholders were involved in developing the Principles and that is why it is such a comprehensive and high-level document. The Principles grew out of the opinions of all the stakeholders who contributed to the paper.

As to why there are ten Principles, that was a rather personal decision between me and one or two others. There was a feeling that this was a really important document and that ten was a good number. It could have been 12 Principles, but Europe works on a decimal rather than a duodecimal system and we were not dealing with imperial measures. After all the British Empire is finished 😊

RM: Can you talk briefly about the process of establishing the Principles?

BC: *What happened was that I was asked to chair a meeting with a large number of European key opinion leaders who were physicians, plus people from the EHC and nursing staff. We started, really, from very basic principles, where everybody said what they thought was important. We didn't look at any documents at all; we just brainstormed the issue. Then, in subsequent meetings we put our ideas in order and developed a set of organised principles. It was very much what nowadays is called a "bottom-up" process.*

RM: What is the difference between 'Principles' and 'Guidelines'?

BC: In my mind, principles are "broad brush" but guidelines are more specific. If you are thinking of road safety, we all think it is important that we shouldn't have road crashes but which side of the road you drive on is a matter of choice. The British drive on the left, mainland Europeans drive on the right (and the Maltese say that they drive in the shade!) So, road safety (fixed idea) is a principle and the highway code (which side of the road to drive on) is a guideline.

Now in terms of haemophilia, for example, the concept of "provision of prophylaxis" is a principle which doesn't change, while the dosage and frequency of treatment is a guideline, which may differ from country to country, depending on availability of treatment. Provision of sufficient safe therapy is a principle, but exactly what product to use e.g. recombinant versus plasma derived, is a guideline matter.

If the condition was cured then, perhaps, home treatment might no longer be a necessary principle but it was a central pillar of treatment between the 1970s and today.

RM: What was the haemophilia landscape like at the time of establishing the Principles?

When I was Chairman of the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO), I was involved with some dialogue within Europe but it didn't go anywhere. I think that the decision by Professor Mannucci, Professor Ludlam and Dr Astermark to make further progress started in 2005 and it was just the right moment to bring Europe together. At this time, the Eastern bloc had changed enormously, a number of countries in the East were getting ready for a more advanced haemophilia care and Romania and Bulgaria were preparing for accession to the European Union. Some European countries were producing their own guidance but there were no European Principles. The nature and quality of care in Europe was very varied, especially as the former Eastern European countries emerged (and indeed Russia has put much effort into haemophilia care). The Principles were partly designed to help emerging countries to persuade their governments, carers and patients of the need to support people with haemophilia, but without introducing unachievable goals.

It is important to appreciate that, as we began to develop a more European view of haemophilia care and tried to bring everybody up to a good standard, it was also the case that we never thought that this was purely confined to the European Union. These Principles have now been looked at all over the world. It was a European initiative, it was designed to bring Europe together, but we had a lot of influence from other European countries and we never intended this to be a purely European Union phenomenon.

RM: Do you envision "comprehensive care" taking on a new meaning with the emergence of novel therapies?

The ideal of looking after people with haemophilia in a comprehensive way cannot change. If there were to be, (in fact there will be), a cure for people with haemophilia, then we can all go home. But I don't think that that is going to happen for quite a long time. In the meantime, the new treatments for haemophilia will need to be looked at very carefully, they will need to be regulated, rolled out in the right way, and then properly assessed. Any adverse events must be recorded. All that work will continue to be under the influence of the European Principles and of course, the European associations that deal with side effects and the quality of care. The EHC is absolutely critical in delivering that because, as you know, Brian O'Mahony and his colleagues have been particularly active in analyzing what European Principles really mean and what effect they have had.

The EHC marked World Haemophilia Day 2018 with an event theme of 'Principles and Partnerships', based on the ten years since the publication of the European Principles of Haemophilia Care. Read the highlights from the event on page 31.

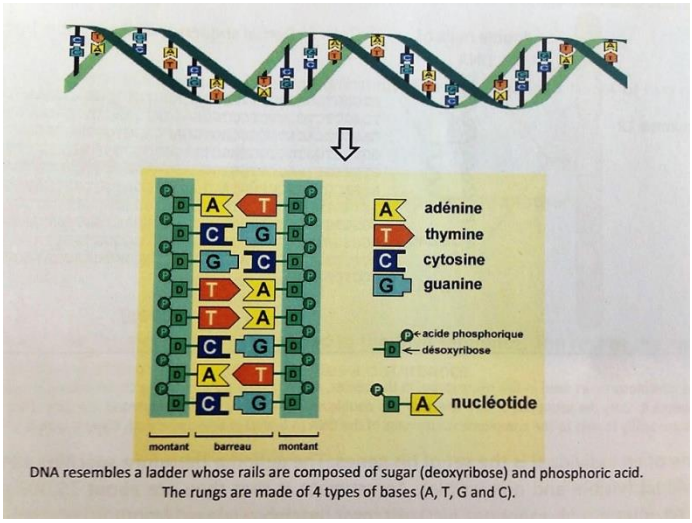
Exploring the Fascinating World of Généthon – Part I

By Raia Mihaylova, EHC Communications Officer

From February 13th-15th, EHC staff and members of the EHC Steering Committee entered the fascinating world of Généthon – a laboratory in Evry, France, dedicated to advancing gene therapy treatments for rare diseases. Since its creation in 1990, work done at Généthon has greatly contributed to understanding and decoding human genes – the regions of our DNA that contain the information needed to make proteins or other molecules essential for the growth and functioning of an organism. The 200+ researchers, pharmacists, doctors, bioproduction engineers and technicians that work there continuously build on academic discoveries to develop them into gene therapy treatments for patients. There are currently 6,000-8,000 known rare diseases, 80 per cent of which are genetic in origin.

As gene therapy holds many of the answers that the haemophilia community has long searched for and could even be a potential cure, we in turn had many questions on how it works and what its challenges and successes look like. We signed up for training at Généthon with the aim to understand more about this exciting novelty and to be able to better break-down the concept to patients and our national member organisations. To comprehend its complexity, we were first introduced in-depth to cells, chromosomes, sequencing, amino acids, proteins and more head-spinning human components that are so complex, they make you want to pull your DNA (present in hair) out.

It all starts with cells, which are the basic unit that makes up all living things. Each cell contains the same genetic information, which is located in the cell nucleus and is in the form of small structures called chromosomes. Humans have 23 pairs of chromosomes that we inherit from our parents and that determine our sex, eye and skin colour, susceptibility to diseases and many other genetic traits that make us who we are. The chromosomes themselves are composed of threads of DNA whose "language" is decoded by mapping out the sequencing of four chemical substances called nucleotides or bases – adenine (A), thymine (T), cytosine (C) and guanine (G). In each of our cells, our DNA is composed of about three billion of these **base pairs**. Without getting ahead of ourselves, it is a mutation, which we learned can happen in several ways, in the order of the base pairs that causes genetic diseases.



DNA takes the form of a double helix structure, which if rolled out, looks like a ladder. The base pairs form the "steps" of the ladder and contain the genetic information; they always pair in the same way – adenine with thymine (AT) and cytosine with guanine (CG).

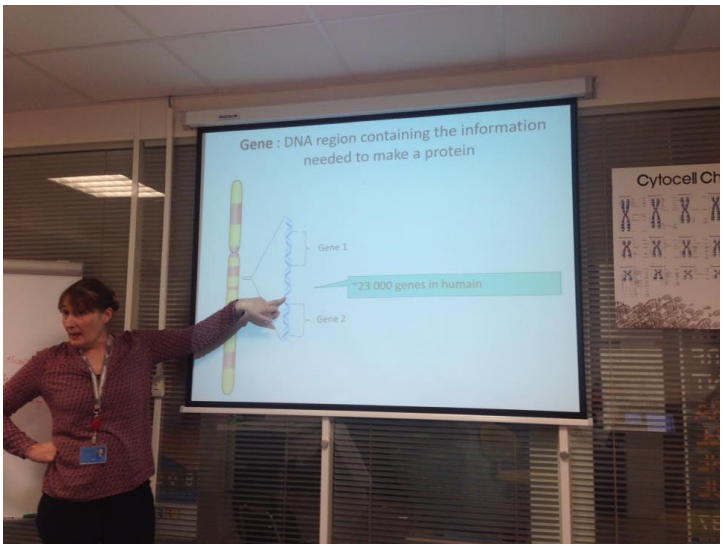
To help us visualise these concepts better, our trainers at Généthon had us do a series of experiments. Our first task was to isolate our own DNA from our saliva, which is surprisingly easy and can be done even at home by adding dishwashing liquid, a pinch of salt and rubbing alcohol. Another experiment was isolating

DNA from saliva cells.

a specific area of our DNA and amplifying it in order to analyse the number of base pairs located there. In the general population, this particular DNA fragment either contains 100 base pairs or 400. The experiment showed that we were a very homogenous group, as it concluded that all of us had the short version of the fragment, with 100 base pairs. Claire Rochette, Head of Scientific Mediation and the School of DNA at Généthon, speaks in more detail of the experiments we did in the three days and their lead up to learning about gene therapy.

RM: We did a lot and learned a lot in these three days. Before we even got to the topic of gene therapy, there were a lot of other concepts we had to cover first. Can you summarise briefly what we did here? We started with learning about cells, chromosomes, DNA…

CR: *Exactly, to help you learn more about DNA, we had you extract your DNA from your own cells in the mouth. And you were able to see your DNA like a jelly fish in the test tube. The day after, you analysed your DNA and eventually amplified it in order to see if there is a mutation on it. Another experiment you did was putting a green fluorescent protein (GFP) in bacteria to see the link between DNA and a protein. To make a protein, you need a gene, which holds the information. You can put a gene in bacteria, which is a cell, to produce a protein. And this new information changes the phenotype of the bacteria.*



Claire Rochette explains what the function of a gene is.

This is the same method used by pharmaceutical companies to produce coagulation factor. They put DNA coding for factor VIII in bacteria, or yeast, or stem cells, and they produce human factor for coagulation as you did with the GFP protein.

RM: Gene therapy in haemophilia is a relatively new concept but it actually goes further back. When did gene therapy in general start being talked about / how did gene therapy come to be?

CR: *In France, the first test with gene therapy in a human was in Necker Hospital done by Alain Fischer, a clinical researcher. He treated nine children with a special rare disease of the white blood cells called severe combined immune deficiency (SCID) ADA (marked by a deficiency in the enzyme adenosine deaminase). It was in the 2000s. And now for haemophilia the first trial in men was started in 2010, so ten years after.*

RM: In very simple terms, can you explain what gene therapy is?

CR: *Gene therapy is the way to insert DNA that has no mutation into the nucleus of the cells that need to be treated. The DNA has to be inserted somehow – if you put DNA on your skin, it doesn't absorb into your*

cells. So you have to pack the DNA into virus vectors, which is a capsid, a box, with the new gene in it. This has the capability to go through the cells into the nucleus to deliver the new gene. And then cells are capable of producing the protein, which they were not capable of doing before. This is gene therapy. For haemophilia, the proteins for clotting factor are produced in the liver so we target the liver cells to produce the factor for coagulation.

In part II of 'Exploring the Fascinating World of Généthon,' we talk to Elena Barbon, who holds a PostDoc position at Genethon and focuses on developing gene therapy strategies for bleeding disorders. She explains to us recent achievements and challenges of gene therapy for haemophilia and von Willebrand disease (vWD).

Exploring the Fascinating World of Généthon – Part II

By Raia Mihaylova, EHC Communications Officer

In the first part of the material on our visit to Généthon, we explored the basic unit of all living things – the cell. When explaining their function, scientists often refer to cells as miniature factories with storage, transportation and communication departments, as everything the body needs to function is produced there. For example, the cell nucleus, or the CEO office, contains our DNA. A particular fragment of the DNA stores the instructions needed to produce a protein, such as the clotting factor protein. This fragment is known as the gene.

Each of our cells is constantly dividing and replicating into two daughter cells. This process of division is called mitosis, but before it happens, the cell DNA has to be copied so that each new cell receives a full set of instructions on how to function**.** Each time mitosis occurs, a mutation in the sequencing of the DNA base pairs adenine (A), thymine (T), cytosine (C) and guanine (G) can take place, in the form of either substitution, insertion or deletion. Most often, the mutation is insignificant but in other cases, it could lead to the creation of a defective gene.

As explained at Genethon, genetic disorders, such as haemophilia, are caused by a defective gene that prevents the production of a fully functional protein. Therefore, gene therapy involves inserting a normal gene into the cell, so that it can make the missing or deficient protein. To transfer the gene, scientists use what is called a vector, or a virus that is rendered harmless, which has the capability to go through the cell wall into the nucleus and deliver the new gene. This way the cells are capable to produce a fully functional gene.

Elena Barbon, who holds a PostDoc position at Généthon and focuses on developing gene therapy strategies for bleeding disorders, explains recent achievements and challenges of gene therapy for haemophilia and von Willebrand disease (vWD):

Elena Barbon talks gene therapy and the challenges ahead.

EB: *Gene therapy for haemophilia is progressing, I can say, really fast but there are still some challenges we have to take into account. The first one is the immune response. When you inject the viral vector you can have an immune response from the body against the vector that you infuse or against the therapeutic gene. So now, research is really focused on how to avoid or to escape the immune response in order to permit the re-injection of the vector, especially if we think about peadiatric patients.*

RM: For haemophilia A, it is more challenging because of the size of the gene….

EB: *Yes, the size of the gene is a problem because the normal gene doesn't fit in a viral vector but for now, we have solved the problem by putting a modified version of the protein. The other problem for haemophilia A is that factor VIII is less expressed compared to factor IX, so it is poorly circulated into the system. The*

levels that we obtain are lower compared to factor IX, so to have the same efficacy, you need to really increase the dose of the vector, but there is the consequent problem in term of immune response. Because when you increase the dose, we increase the risk for a response from the immune system.

The story is much more complicated for von Willebrand factor because we have still not reached an optimal viral vector to deliver the gene, which is quite big and doesn't fit in a single adenovirus vector. One of the strategies we can use is to use two different adenovirus vectors to deliver the therapeutic gene. Of course, this is not a super efficient way to work, because you need to have the co-infection of two viruses, which are the same in size, to have the von Willebrand factor expressed.

Another issue is that von Willebrand factor is naturally expressed in the endothelial cells, which is the natural biosynthetic site. The expression and the regulation of the protein is quite complex so what we need to do is to really find out the way to target the endothelial cells in a way we can express von Willebrand factor in a proper manner.

Elena's prognosis as to when gene therapy will be widely available for haemophilia patients is in 10-15 years' time. Until then, it is of extreme importance to gather data on the safety, efficacy and possible side-effects that gene therapy could have.

The EHC thanks Claire Rochette and Elena Barbon for the interesting and in-depth training on gene therapy and the important works of Généthon.

2018 EAHAD CONGRESS

Attended and covered by Declan Noone, EHC PARTNERS project consultant and Radoslaw Kaczmarek, EHC Steering Committee member

Welcome to Madrid, where the 2018 Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) took place from 7th-9th February. The Congress brings more than a thousand leading medical experts and patients together to exchange on the latest updates and information in treatment and care for the disorders represented by EAHAD.

In the following conversation, Declan Noone, EHC PARTNERS project consultant, and Dr Radoslaw Kaczmarek, EHC Steering Committee member, share what talks they found interesting and their views on the conclusions made. Ahead of their impressions, you can first find a short summary of the referenced presentations.

Talk: Can we now forget about Hepatitis C (HCV) in haemophilia?	**Speaker: Dr Juan Berenguer, HIV Infectious Disease Unit, Madrid, Spain**

Summary:
After more than a decade in which interferon plus ribavirin (RBV) was the mainstay of anti-HCV therapy, the introduction of direct-acting antiviral agents (DAAs) represents a breakthrough in the treatment of infection by HCV. This therapeutic advance provided new opportunities for the treatment of patients with haemophilia, a population group at risk for the significant morbidity and mortality associated with HCV infection. Data from clinical trials or real-world studies on HCV treatment with DAAs in patients with haemophilia are scarce. However, over the last two years, some trials have shown high efficacy and

safety of the fixed-dose combinations of ledipasvir with sofosbuvir (LDV/SOF) and grazoprevir/elbasvir (GZR/EBV) for patients with inherited blood disorders including hemophilia. Currently, the majority of patients with haemophilia and HCV can expect to achieve sustained viral response independently of the infecting HCV genotype and the stage of liver disease. However, long-term follow-up studies will be necessary before we can fully appreciate the impact of successful therapy in patients with cirrhosis regarding developing liver cancer or liver failure and the need for liver transplantation.

DN: *From my perspective, one of the most interesting presentations was the talk on hepatitis C and the importance of not forgetting those patients.*

RK: *Yes, it was provocatively titled "Can we forget about Hep C" and the answer actually was "yes." But you have to remember that a risk for hepatocellular carcinoma remains, even for people who achieve sustained virological response (SVR), but especially if there was liver cirrhosis before getting on therapy. So it is important to monitor.*

Presentation: Intracranial haemorrhage in inherited bleeding disorders	**Speaker: Ri Liesner, Consultant in Paediatric Haemostasis and Thrombosis**

Summary:
Intracranial haemorrhage (ICH) is the most devastating complication affecting patients with inherited bleeding disorders (IBDs). It is associated with a significant risk of mortality and morbidity with many affected individuals having long-term neurological sequelae. Cohort studies suggest incidences of 3%-5% in severe haemophilia but higher rates are seen in the rarer bleeding disorders (factor II, V, VII, X and XIII deficiencies).

ICH can be the presenting symptom in previously undiagnosed cases of IBD, not uncommonly in the neonatal period as a result of birth trauma. Cases that present later in infancy or childhood can occur after minimal or no apparent trauma. In known severe IBD babies, parents should be educated on the early signs of bleeding and when to ask for urgent help. Ideally, they should also always have a small supply of factor concentrate replacement for clinicians to be able to treat in an emergency, as early treatment reduces mortality risk and morbidity.

The risk of ICH in the rarer severe bleeding disorders prompts treaters to consider prophylaxis from early infancy particularly if an ICH has already occurred or the infant has declared its severe phenotype by presenting with other bleeding such as umbilical cord bleeding. However, this always presents challenges with venous access difficulties in this young age group. In haemophilia, prophylaxis has been proven to reduce musculo-skeletal bleeding problems but a recent multicentre study (*Andersson et al BJH 2017*) showed that it also significantly reduces the ICH risk — this is a less well recognised benefit of prophylaxis. In this study the ICHs in the on- demand group had an 8% mortality and a third had long term neurological sequelae.

The treatment of an ICH event that has occurred requires prolonged high dose factor concentrate treatment to treat the bleed and prevent recurrence. In haemophilia A this intensive factor exposure is a recognised risk factor for inhibitor formation and the subsequent development of an inhibitor makes on-going treatment more demanding and usually very expensive.

Although the majority of the data available on ICH in bleeding disorders is in neonates and young children it is recognised that there is ongoing risk through into adulthood and older age where individuals may not be compliant on regular prophylaxis and falls become more commonplace. Increasing awareness and education is as important in this older age group as it is in parents of young babies with bleeding disorders.

RK: *To me, the 'Intracranial haemorrhage in inherited bleeding disorders' talk was one of the greatest highlights of the day it was presented on. It was a very compelling talk because haemorrhage sort of goes under the radar, yet there are many problems that need to be addressed. If you come to think about it, there is a 20-40 per cent of mortality among people with haemophilia who suffer intracranial bleeds. This goes to show that you have to do your best to prevent it and one of the best ways to do that is first, to be on prophylaxis and second, to keep in check additional risk factors, such as hypertension, which is prevalent in the population of people with haemophilia.*

Presentation: Women's issues in inherited bleeding disorders	**Speaker: Professor Sophie Susen, Department of Haematology Transfusion, Lille University Hospital, Lille, France**

Summary:
Throughout their lives, women have to face more haemostatic challenges than men, because of menstrual bleeding and during pregnancy. Health related quality of life is especially impacted in women with inherited bleeding disorders (IBD).

Heavy menstrual bleeding is the most common symptom in the IBD female population. It can be the first clinical sign leading to the diagnosis of IBD and is included in Bleeding Assessment Tools. Indeed, among the first family described by Eric von Willebrand in 1926 was a teenager who died aged 13 of menorrhagia. It affects 32 to 100% of women with von Willebrand Diseases (VWD), 5 to 98% of women with platelet dysfunction and 35%-70% of women with rare factor deficiencies. Menorrhagia induce limitation in daily activities, absenteeism from work or school, and reduced quality of life compared to women with normal haemostasis, especially in women with VWD. They can lead to iron deficiency and anemia and require hormonal therapy, antifibrinolytics, iron supplementation, and in the most severe cases require replacement therapy, desmopressin, red blood cell transfusion or platelet transfusion in inherited platelet function disorders such as Glanzmann Thrombasthenia. It can be an indication for long term von Willebrand Factor prophylaxis. Local treatment may also be necessary, such as curettage, endometrial ablation or even hysterectomy.

During pregnancy, care is more complex. Coagulation factor levels should be checked around 34 weeks of gestation, as some may rise sufficiently to allow delivery without replacement therapy (VWF, FVIII, FVII, FX, and fibrinogen). Invasive procedures during pregnancy, including prenatal diagnosis of the IBD, may require replacement therapy, a single desmopressin injection or blood transfusion.

Delivery and puerperium is at higher risk of post-partum haemorrhage (PPH) in these women (three-fold in VWD) and requires a specialised and multidisciplinary approach. Delivery should take place, especially in severe and rare cases, in a tertiary center with an obstetric unit that can quickly access Haemophilia Center and comprehensive neonatal care facilities, bearing in mind that the child can also be affected with an IBD and be at risk of neonatal bleeding. A management plan should be drawn prior

to delivery, both for the mother, regarding neuraxial anesthesia and post-partum haemorrhage management, and the child, regarding invasive monitoring procedures, forceps and vacuum extraction contraindication. There is no consensus on the safest method of delivery. It should be the least traumatic and early recourse to c-section should be considered to minimize the risk of neonatal bleeding complications. Use of syntocin, iron therapy, antifibrinolytics, replacement therapy, desmopressin, and sometimes red blood cell transfusion or platelet transfusion might be required in case of PPH. Examination under anesthesia or use of uterine balloon and in the most severe cases internal iliac artery legation, uterine artery embolization, uterine brace sutures or even hysterectomy might be required. Thromboprophylaxis should be considered in case of replacement therapy, either pharmacological or mechanical.

DN: *The EHC is carrying out a 'Women and Bleeding Disorders' survey this year and it was interesting to hear the talk from Dr Susen on "Women's issues in inherited bleeding disorders." It was very comprehensive. She covered the importance of heavy menstrual bleeding and the impact it has on carriers, von Willebrand's patients and Glanzmann's patients. We need to do more to try and improve the care for women with bleeding disorders.*

Presentation: Phase 1/2 trial of single and multiple dose subcutaneously administered factor IX variant CB 2679d/ISU304: Pharmacokinetics, activity and safety.	**Speaker: Dr Howard Levy, Chief Medical Officer at Catalyst Biosciences**

RK: *I was really interested in the talk on "Phase 1 / 2 trial of single and multiple dose subcutaneously administered factor IX variant," which is a great potential for that drug. It is in early trial results, phase 1/2, so it is very early in development but to me, the most compelling thing is the degree to which the half-life has been extended — not just because how the drug was modified to achieve that but also because of the mode of administration. Actually, the subcutaneous administration extends the half-life from 27 to 63.5 hours, so it shows the great potential for subcutaneous factor IX.*

Presentation: Gene therapy for haemophilia: an update	**Speaker: Professor Frank Leebeek, Erasmus University Medical Centre, Rotterdam, Netherlands**

Summary:
In the last decade an enormous progress has been made in the development and therapeutic use of gene therapy in haemophilia. In most studies a modified inactivated Adeno-Associated Virus (AAV) vector with the wild-type coagulation factor gene inserted is used. The vector is given intravenously as a single infusion and migrates to the host liver which results in expression and synthesis of the missing coagulation factor and increase of FVIII or FIX in the circulation. To date only one study has been published with long-term results of gene therapy in haemophilia B. Using an AAV8-based vector, patients had expression levels of 5-10 IU/dL depending upon the infused dose of gene copies. This resulted in a dramatic decrease in number of bleeds, use of coagulation factor concentrates and the need for prophylactic infusions. At long term follow-up of at least six years, these patients still have expression of FIX, without reduction of expression levels over time. Currently more than ten studies on gene therapy

in haemophilia are ongoing or planned and of some of these studies preliminary results have been presented. The results of an AAV5 based FIX gene therapy trial gave similar results as the AAV8 based studies. This is of interest because only a small minority of haemophilia patients have a pre-existent antibody response to AAV5, whereas up to 40% may have antibodies against AAV8, which makes them ineligible for gene therapy with this vector. An interesting improvement of gene therapy in haemophilia B patients is accomplished by the use of a modified FIX gene, based on the naturally occurring FIX Padua variant, which has a 7-8 fold higher specific activity than wild-type FIX. Use of the Padua variant in gene therapy resulted in FIX activity of around 30-40 IU/dL. Recently also the first results of gene therapy for haemophilia A were presented. The patients treated in this study with AAV5 based vector containing wild type FVIII gene resulted in high expression levels, even up to normal FVIII levels in the majority of patients. This led to a clinical improvement and most patients did not report any bleed after gene therapy. Unfortunately, not all gene therapy studies are successful. One study reported recently showed loss of expression of Factor IX in seven out of eight patients after gene therapy, associated with an immune response to the infused vector. Another problem is the occurrence of immune-mediated liver function test abnormalities, requiring prednisone treatment. Despite these hurdles that have to be overcome, gene therapy is a promising treatment for haemophilia patients, resulting in a lower number of, or even no, bleeds after treatment and reduction of coagulation factor use. Phase III studies are awaited to confirm the promising phase I study results.

DN: *The last session of the day was on "Gene therapy for haemophilia: an update" and it was very exciting to see such progress so quickly and so many clinical studies – 20-21 between haemophilia A and haemophilia B.*

RK: *Yes, the very fact that we have an entire session now devoted to gene therapy is amazing. The results that have so far been achieved are really mesmerizing in terms of the potential of this being a cure.*

DN: *One of my particular things that I would like to see in the phase III trials is the inclusion of patients with HIV, which is very important for our community going forward.*

RK: *Yes, one of the important points of the talk is that investigators are already brainstorming on ways to overcome some of the obstacles that are known, such as the pre-existing immunity against the AAV vectors. Most of the trials that are advanced rely on these viral vectors to deliver the drug in order to achieve the therapeutic effect. And this is a problem in a large portion of the population.*

The 2019 EAHAD Congress will take place in Prague, Czech Republic from 6th-8th of February.

EHC Round Table on Economics and Access, Health Care Systems and Novel Therapies

By Raia Mihaylova, EHC Communications Officer

Novel haemophilia therapies are undoubtedly transforming the current treatment landscape into an opportunity for better health outcomes for patients but also into an area full of unknowns. If there are cost differences between standard half-life (SHL) and extended half-life (EHL) FVIII treatment and it is possible to achieve the same trough levels with both – which will be more economically valued? If increasing the dose of SHL products can mean higher trough levels but EHL products bring the promise of less infusions – are we measuring the right outcomes? If novel medicines can effectively lead to turning severe haemophilia into mild haemophilia – will they undermine the importance of comprehensive care? Along with better efficacy, do they bring risks?

As with every change, moving forward with EHLs, novel non-factor replacement treatments and gene therapy will require, in the first place, education for patients, doctors, policy-makers, pharmaceutical companies and health care workers. To create this network of education, on February 28th, the European Haemophilia Consortium (EHC) held its first-of-the-year Round Table of Stakeholders on the topic of 'Economics and Access, Health Care Systems and Novel Therapies' in the European Parliament. Over 40 participants representing the above-named stakeholders joined the conversation on novel haemophilia treatments and the changing landscape they are bringing on a political and economic level. Chairing the event, Member of the European Parliament (MEP) Norica Nicolai was joined by her colleagues MEPs Dr

Miroslav Mikolášik and Dr Cristian Bușoi in support of the rare bleeding disorders community and to provide input on what political action needs to be taken to effectively steward the research, regulatory and policymaking landscape through this next phase of haemophilia treatment.

> *"With novel therapies, we need to work together to make sure they don't come on top of inequalities but rather are received in a timely manner all over Europe."*
>
> *MEP Miroslav Mikolášik*

Economic theory defines rational behaviour as a decision-making process which is based on making choices that result in the most optimal level of benefits or utility for the individual. So how will novel therapies be economically valued and will the balance between price and patient benefit be weighted in in this estimation? The introduction of EHL products has already changed the way we think about treating patients, mainly from the angle of achieving the same trough levels as with standard treatment products but with less number of infusions. Less infusions could mean less economic burden on the health care system, especially in the long-term.

The differences in outcomes pile up even more when looking at novel treatments and gene therapy. As speakers at the Round Table went through this progression of change (EHL → novel treatments → gene therapy), it was stressed that looking solely at price doesn't accurately portray economic value. With novel therapies, we are in a situation where a patient can move from a life with spontaneous bleeds to a spontaneous life, not having to plan around when their treatment will take place. This in itself is an economic factor and a value that should be part of the equation.

Slide from the presentation of Dr Dan Hart, member of the EHC Medical and Scientific Advisory Board, on 'Opportunities and Threats of Novel Agents'.

It is also important to acknowledge that while discussions around new therapies are crucial, we must not miss the opportunities that the treatments we now have in front of us hold. Current standard of care has brought along increased affordability, availability, access and personalisation of treatment, which was the wish list just a short amount of time ago. Being distracted with what will happen in the years to come threatens optimising these opportunities that have translated from a wish list to reality.

Other questions worth thinking about are whether the haemophilia community is prepared to switch to novel therapies and whether comprehensive care has a future, as novel therapies hold the potential to "downgrade" people with severe haemophilia to the mild form of the condition. And though we are excited to be in a time where we are able to ask these questions, we have to pause and think about how to pave the way for new treatments and how the health care system will adapt to them.

As covered during the Round Table, regulation and legislation policies are working to integrate all these questions early on. But policy is not just about content or competence, it is also about timing. Given the strong political support assured by the attending Members of the European Parliament and the review of several relevant pieces of legislation by the European Commission, there is little doubt that novel therapies will politically find a home.

Members of the European Parliament Group on Rare Bleeding Disorders

Written by Raia Mihaylova, EHC Communications Officer

In November 2017, the European Haemophilia Consortium (EHC) formalised its Member of the European Parliament (MEP) Group on Rare Bleeding Disorders. Created so that the challenges of haemophilia and other rare bleeding disorders are met with a coordinated political response, its members include MEPs **Norica Nicolai** (ALDE, Romania), **Ms Nessa Childers** (S&D, Ireland), **Dr Cristian Bușoi** (EPP, Romania), **Dr Miroslav Mikolášik** (EPP, Slovakia) and **Mr Heinz Becker** (EPP, Austria).

Coming together for the first time since then, members of the group attended and spoke at the first 2018 EHC Round Table on 'Economics and Access, Health Care Systems and Novel Therapies.' The Round Table once again brought a mixture of experiences into the room, with over 40 patients, medical experts, policy makers and pharmaceutical representatives joining the conversation on novel haemophilia treatments and the changing landscape they are bringing on a political and economic level. Chairing and opening the event, MEP Norica Nikolai stressed the need for all patients in Europe to have access to haemophilia treatment and her support in helping to do so. Shortly after, I met with her to speak about why she got involved with the haemophilia community and what she hopes to accomplish with the MEP Group on Rare Bleeding Disorders.

MEP Nikolai: *A few years ago, I remember in Bucharest, I participated in a TV show with two guys coming from Romania and who had haemophilia. It was the first time that I saw that in my country there are people in need, that there are sick people that are ignored. Before that I knew some things about haemophilia, but I had never faced a person who had it.*

I am proud to serve this community because I understand people. All of us need to have the right to a normal life and for me, as a politician, its normal to support this necessity of the people.

MEP Norica Nikolai chaired the EHC Round Table on Economics and Access, Health Care Systems and Novel Therapies.

RM: You are a member of the MEP Group on Rare Bleeding Disorders, what do you hope to accomplish as a group and what are the objectives?

MEP Nikolai: *We want to continue to raise the awareness of the European community and also, because we expect new revisions on the legislation. We have 2-3 pieces of legislation that are relevant to the haemophilia community. We are able to work with the community in order to improve the mechanism for support for people with haemophilia and to continue to educate and to speak about this condition to all people. Because to survive, they need the support of the entire society.*

MEP Dr Miroslav Mikolášik

Also present at the Round Table were two other members of the group, MEP Dr Cristian Bușoi and MEP Dr Miroslav Mikolášik. Both showed determination in taking political action to effectively address the challenges of the haemophilia community:

MEP Miroslav Mikolášik: *"Being a doctor myself, I know that patients do not have equal access to adequate medical care across Europe. With the Rare Bleeding Disorders Group being formalised, we have made a substantial step forward and I see the group as an amplifier to mobilise*

even more colleagues in the European Parliament to provide a real tangible and coordinated support and most importantly, to move from discussions to action."

MEP Dr Cristian Bușoi has supported various EHC events throughout the years.

MEP Cristian Bușoi: *"I know that we need a better understanding economically and politically in order to improve the quality of life of people with rare bleeding disorders. We have many opportunities here, but we also have a lot of challenges, a lot of complicated situations, mostly in Central and Eastern European countries. I believe we can improve the situation for haemophilia and other rare bleeding disorder patients only if we have a vision and only if we truly understand the needs of patients before anything else."*

An MEP group work plan on addressing challenges of the rare bleeding disorders community across Europe will soon be developed and published.

MEP Dr Heinz Becker

MEP Nessa Childers

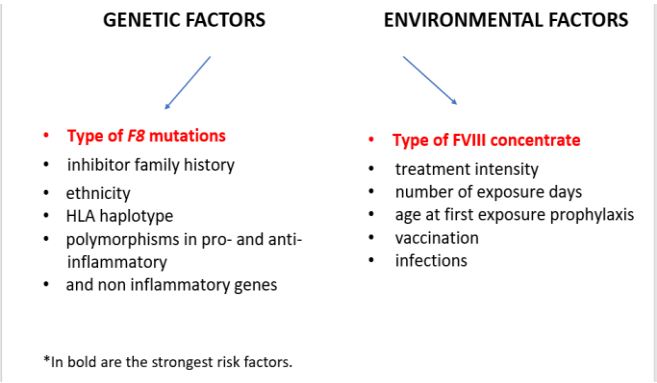
The EHC expressed gratitude to MEPs Norica Nicolai, Nessa Childers, Cristian Bușoi, Miroslav Mikolášik, and Heinz Becker for their valuable support to the haemophilia and other rare bleeding disorders communities.

Inhibitors in their **ENTIRE**ty: presenting the European Network on Inhibitor Research Group

By Raia Mihaylova, EHC Communications Officer

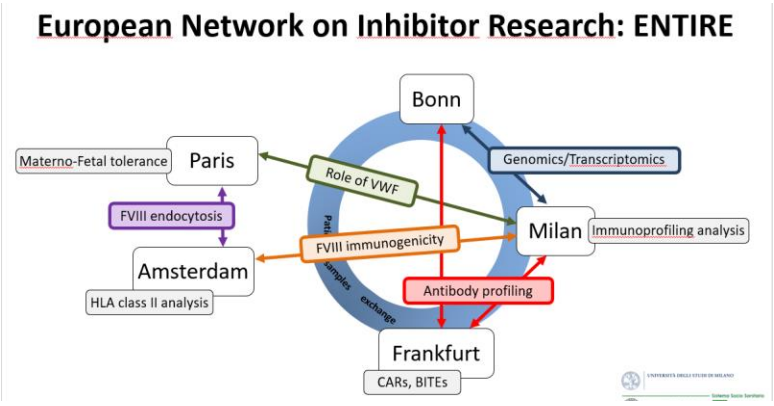
When speaking of novel haemophilia agents, there is a re-occurring phrase often used to describe their effect – "changing the haemophilia landscape." Extended half-life products have already led to significant improvements and together with other emerging novel therapies, are allowing patients to reduce the number of weekly injections while increasing protection from bleeds, as well as decreasing joint damage and pain.

If the definition of a landscape in this case is "*the distinctive features of a sphere of activity*," there is one attribute that has stubbornly stuck throughout the years – inhibitor development and the unknowns around it. A complex complication, inhibitor development results from interaction between the genetic and environmental risk factors of patients. It is interesting to note that in the case of haemophilia A, it is not that certain patients develop an immune response to their factor VIII treatment (FVIII) and others don't, but rather the other way around – all haemophilia A patients have an immune response to FVIII but 70-95 per cent of them will develop tolerance. So why don't the remaining patients?



Information taken from Professor Flora Peyvandi's presentation at the 2018 Inhibitor Conference in Milan.

As an answer to that question, Professor Flora Peyvandi from the Angelo Bianchi Bonomi Haemophilia and Thrombosis Center in Milan, and member of the EHC Medical Advisory Group, formed a multidisciplinary team to address the complex interplay between patients' genetic and environmental-related risk factors, and to try to prevent inhibitor development and develop innovative protocols for inhibitor eradication in patients with haemophilia A. The European Network on Inhibitor Research, or ENTIRE, brings together leading experts from various fields and universities, each specialising on concrete research. This will allow for the exchange of different human biological samples between the group, which are collected during a biopsy or surgery and are preserved by researchers to study the specifics and progression of a disease. The ENTIRE studies cover and focus on the role of the von Willebrand factor (vWF), FVIII immunogenicity, antibody profiling and genomics/transcriptomics analyses.



Slide from Professor Flora Peyvandi's presentation at the 2018 Inhibitor Conference in Milan.

"*This is the first European network that tries to empower the biological sample collection among centres and to bring together expertise and knowledge at European level in order to understand the pathophysiology, to predict, and to eradicate the inhibitor in haemophilia*," explains Prof Peyvandi.

The ENTIRE group includes **Sebastien Lacroix-Desmazes** from France; **Christoph Königs** and **Johannes Oldenburg** from Germany; and **Frits Rosendaal** and **Jan Voorberg** from the Netherlands.

Flora Peyvandi, MD, PhD

Professor of Internal Medicine at the University of Milan and Director of the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Milan, Italy

Christoph Königs, MD, PhD

Clinical and Molecular Haemostasis, Department of Pediatrics at the University Hospital Frankfurt and Goethe University Frankfurt, Germany

Sébastien Lacroix-Desmazes, MD, PhD

Cordeliers Research Centre Paris, France

Johannes Oldenburg, MD, PhD

Institute of Experimental Haematology and Transfusion Medicine University Clinic of Bonn, Germany

Jan Voorberg, MD, PhD

Head of the Cellular Haemostasis Laboratory Sanquin Research Amsterdam, Netherlands

Frits Rosendaal, MD, PhD

Professor of Clinical Epidemiology and Head of the Clinical Epidemiology Department Leiden University Medical Center, Netherlands

When asked about his vision for ENTIRE, Prof Rosendaal credits the diversity of the group as what is needed to really tackle the multi-causal factors behind inhibitor development:

"*The inhibitor problem is currently the major complication of haemophilia treatment, and its incidence has only gone up over the last decades. I hope that by bringing together experts with quite different backgrounds, based in biochemistry, immunology, genetics and epidemiology, we can come to truly translational research that will lead first to better understanding, and then to improved prevention and treatment.*"

As to the philosophy behind it, Dr Sébastien Lacroix-Desmazes shares that by fostering the development of common research projects, the group aims to understand the etiology of the development of inhibitor antibodies to FVIII from both a patients' and a products' perspective, and to imagine and validate novel strategies to induce long-term tolerance to therapeutic factor VIII:

"The ENTIRE research group is a European initiative from leading academic research teams working on the immunogenicity of therapeutic pro-coagulant factor VIII in patients with haemophilia A. The inclusion

in the ENTIRE research group of basic scientists and clinicians creates a multidisciplinary group ideal for intellectual discussions and exchange of ideas and biological material; it promotes synergy between fundamental science and translational research. Importantly, the group brings together a large array of complementary technologies and know-how, including the use of preclinical models and access to patients' biological samples. The creation of the ENTIRE research group will give visibility to research on factor VIII at the European and world-wide levels. The ENTIRE research group aims at influencing decision makers at the national and European levels, and at attracting the interest of funding bodies from both the academic and private sectors."

With years of slow advancement in understanding inhibitor development, the establishment of the ENTIRE research group offers hope where it was lacking before. Together with the improvements brought by novel therapies, there is potential to visualise a fully changed landscape with the new attribute being a high quality of life for all patients with haemophilia (and inhibitors).

Meet the members of the newly formed EHC Women and Bleeding Disorders Committee – Part I

Interviews with Yannick Collé, member of Association Française des Hémophiles, EHC French NMO, Evelyn Grimberg, member of Nederlandse Vereniging van Hemofilie-Patiënten, EHC Dutch NMO, Marion Brauer, member of Österreichischen Hämophilie Gesellschaft, EHC Austrian NMO, and Rose, Ozdemir, member of the UK Haemophilia Society, EHC UK NMO; Interviews were taken by Raia Mihaylova, EHC Communications Officer

In the beginning of 2018, the European Haemophilia Consortium (EHC) established the Women and Bleeding Disorders Committee in order to spread awareness and address the challenges faced by this part of the community. Each member has brought a set of diverse ideas, energy, experiences and determination to ensure that these challenges are paid attention to and acted upon. Through the following interviews, meet Yannick Collé from France, Evelyn Grimberg from the Netherlands, Marion Brauer from Austria and Rose Ozdemir who is Kurdish and originally from Turkey, but has grown up in the UK (*pictured in the listed order*).

RM: *What is your favorite thing about your country or city?*

Evelyn (Netherlands): People only know Amsterdam but there is a lot more to see and do in the Netherlands. You have different areas with different types of nature. I also love that people are very open, we are open to talking about what we think and what we want in life.

Marion (Austria): Vienna has a lot to offer. Culturally speaking, it is an interesting city, there is a lot to explore. That's what I like, it's never boring!

Rose (UK): London is very diverse. There are many types of food from different type of cultures…

Yannick (France): I live in a small village named Sanary and I very much enjoy going along the harbour and seeing the boats, enjoying the quiet places and walking around the beach.

RM: *Why did you decide to join the Women and Bleeding Disorders Committee and what do you hope to accomplish together?*

Evelyn: I got involved because I needed to get in contact with other people with bleeding disorders after having a hard time during puberty. Since that time, I started working on getting more information on women with bleeding disorders and I got to know more people throughout the years from other patient organisations or during European conferences. I think it is important to get together and share our information and knowledge that we already have. If you do it on a European level, I think we can arrange and accomplish more than if you do it just on a local basis.

Rose: Before I applied for my role here (UK Haemophilia Society, EHC UK NMO), they had a project named "Talking Red," which caught my attention. Previously, I had worked with domestically abused women and immigrants and the whole status of vulnerability of women. So, I have always kind of dealt with women issues throughout my life. So, I thought "Okay 'Talking Red,' they are raising awareness around women," and I wanted to get involved and find out more about what they were doing. And I stayed. I now want to empower women in the sense that I want them to be educated about their condition and that they know enough about it so that they are confident and can explain it to someone else. It starts with the empowerment and they can spread that within the community.

Marion: I really would like to raise awareness about women with bleeding disorders because I have learned that, at least in Austria, it's not really a thing that people know about. This includes doctors, and I would like to change that with the help of the committee.

Yannick: Together I think we can be stronger and share ideas and create tools and actions.

RM: *What is one challenge faced by women with bleeding disorders in your country or through your own experience?*

Rose: It would be the mental support that they get, or that they don't get, really. A lot of them experience a lot of emotions. Some will have children with bleeding disorders so they are dealing with the diagnosis, they are going through acceptance. Some are trying to cope with their own bleeding disorders – the relationships they have can be problematic, family relationships, romantic relationships. It impacts every part of their life. But for some reason, the psychological support system is not there. It is difficult to deal with a chronic bleeding disorder that you know is not going to go away, it's not a phase you go into and then you come out of, it's there your whole life. Even that, dealing with accepting that, is a struggle that people overlook. So, I think psychological support is a massive issue.

Marion: My experience is that I usually have to explain what I have [to medical professionals]. I have severe factor VII deficiency and when I tell that to a new doctor I go to, they usually don't know what that means. I have to explain and it is kind of hard because I don't know all the details. Every person has a specific type of deficiency and it is hard to know all about it and tell others about it. I also had the experience that some doctors at first didn't believe that I have a bleeding disorder, they didn't see a connection between

the bleeding disorder and my symptoms. For example, my stomach ache when I had internal bleeding. In that case, it is hard to tell someone who has studied medicine that I know better. That's a tricky thing.

Evelyn: There is the diagnosis and treatment part. I was diagnosed very young, I was four months old, but even for me, it is difficult to get the right treatment. I have Glanzmann's Thrombasthenia and I don't have that many treatment options for my bleeding disorder. But I do have bleeds, especially with the feminine part, if you have a heavy period, there are not that many options besides hormonal options to treat the bleedings. That was a big issue for me. now it is kind of okay but there are also a lot of questions for my future. That's not a question that only I have, there are so many women that have questions about their future reproduction or have gotten a hysterectomy at a very young age so they can't have any children or they don't know how the heredity works, if they can pass it on to their children or not. There is so much that is not being told to them on this subject – I think we know a lot more than we did ten years ago but there are still a lot of things that we don't know and also that we don't tell these women.

Yannick: My biggest challenge was to live with a bleeding disorder for 46 years without knowing I had one. I had to cope with the different bleedings, long periods, bleeding after tooth extractions and things like that. During these moments, no one knew I had a bleeding disorder and it was really difficult for me to live with that. I am a carrier and it's not really a long time ago that it was known or acknowledged that carriers of haemophilia can have bleeds too.

Thank you to Yannick, Marion, Evelyn and Rose for sharing their experiences with the challenges women with bleeding disorders face. In the following article, meet the rest of the committee members!

Meet the members of the newly formed EHC Women and Bleeding Disorders Committee – Part II

Interviews with Tatjana Markovic, member of Udruženje hemofiličara Srbije, EHC Serbian NMO, Naja Skouw-Rasmussen, member of Bløderforening, EHC Danish NMO, and Ana Pastor, member of Associação Portuguesa de Hemofilia e de outras Coagulopatias Congénitas, EHC Portuguese NMO; Interviews by Raia Mihaylova, EHC Communications Officer

Bold, determined and taking action. We introduce to you the remaining members of the EHC Women and Bleeding Disorders Committee – Tatjana Markovic (Serbia), Naja Skouw-Rasmussen (Denmark) and Ana Pastor (Portugal). Ulla Hakkarainen (Finland) was unavailable at the time of the interview (*pictured in the listed order*).

RM: *What is your favorite thing about your country or city?*

Tatjana (Serbia): It is a beautiful country: good hospitality, excellent food. People are nice, very warm and open. We joke a lot, we smile a lot – that is good for our people.

Naja (Denmark): I particularly like Copenhagen, it's a very beautiful city, it is very historical and at the same time, very modern. You have a mixture of a lot of very interesting things.

Ana (Portugal) My favourite thing about my country is the food! It's really amazing, the amount of diversity of the food we have, all of it very good. I also like the landscapes, the fact that we are living in peace, we have lots of sun.

RM: *What is your profession?*

Tatjana: I am teaching math. I give private lessons and it has allowed me to have flexibility. I have a son with severe haemophilia A, now he is 23 years old and he is not a kid, he is a man, of course, but during his whole childhood, I was able to move my lessons around and go to the clinic with him or whatever I needed to do. This was very convenient for me.

Naja: I manage a network for business leaders, business managers, which means I host a lot of meetings where people get together to discuss some of the challenges they have as leaders.

Ana: I am a landscape architect. I do landscape architecture projects in parks, gardens, streets…

RM: *What is one hobby or interest that you have?*

Tatjana: Apart from working?? I have four kids and two grandchildren and you ask me about hobby? (laughing)

Naja: I do try to find some time to do some yoga, to do kite-surfing, to get some fresh air… just to set my mind free. I like to go to concerts or just hang out with people.

The EHC Women and Bleeding Disorders booth at the EHC Conference 2017

Ana: I love dancing, I do Latin and African dances in my free time!

RM: *Why did you decide to join the EHC Women and Bleeding Disorders Committee and what do you hope to accomplish together?*

Tatjana: In many countries in Europe, both the medical and psychosocial aspects for women with haemophilia are on a very low level. Especially the medical aspect, I think the women carriers are completely on the lowest level of treatment and in many countries, they don't recognise us as a category at all. It is very important that we have a committee and the committee can help all the women all over Europe, whether it is through their patient organisations or personally. Women now finally have who to address their questions to.

Naja: From the many years of being in the bleeding disorders community, I keep coming across many women who keep saying that they actually don't know much about their bleeding disorder, that they keep being discriminated against in getting the right education, getting the right treatment, not being taken care of in the proper way. Many of these women are mothers of kids with a bleeding disorder as well.

I think sometimes there is a tendency for a committee to feel as a closed thing and I really want it to be the other way around; that it is something very open, somewhere where we have a lot of discussions and that through our discussions, we educate one another, we learn a lot more and we start raising that awareness that is useful but also educating everyone to have a proper understanding of the challenges. And we can use

the different ideas and the different barriers that people are facing to see how we can work around a certain challenge by getting experiences from different countries.

Ana: Being so different and being women with such different experiences, we can join on a European level and learn from each other and share the information that we have with others who are less informed. And of course, raise awareness.

Part of the EHC Women and Bleeding Disorders Committee

RM: *Can you tell me about one challenge that you as a woman with a bleeding disorder, or as a mother of a child with a bleeding disorder, have faced in your own country?*

Tatjana: In my country, there is a lot of shame in being a carrier. You don't think about yourself, you don't think that maybe you have bleeds too, that maybe you need medical treatment too. We must change this and not be ashamed. We must educate the women, the haemophilia patient, all of society. To make workshops, educate them, and after that, we can do something.

Naja: It is a huge problem that if you only get treated for your symptoms, and you don't get the correct diagnosis, you don't necessarily know that you should get a treatment plan for any other issues that you need to go through. For example, if you have an operation or if you are involved in a car crash, you can end up being in a very severe state because the doctors have no idea that they should treat you in a different way because you have a bleeding disorder.

A lot of people I have talked to, and also what I have experienced myself, is that you go through your life and you have these events of very severe bleeds. For example, with your period or a nose bleed or you get hurt somehow and you need to go to a hospital. And if you again and again meet doctors that don't necessarily take you seriously or don't have the proper background of why you want to be treated in a certain way, you are a little bit left alone. And I think if you talk to a lot of the women in the community, most of them have had the experience where they are trying to tell the doctor that they have a bleeding disorder and the doctor replies "oh no, you don't really" or "it is not that severe so don't be sort of a victim." That creates a huge uncertainty for that particular person, and that is just not good enough. Because as a woman, yes, you have your monthly bleed, but a monthly bleed should not last three weeks every month. And it shouldn't be that you have iron deficiency to such an extent, you can't actually cope. That's not a "women's thing" anymore, it's actually because you have a bleeding disorder.

Ana: We have another problem, it's a political problem. I now know that there are specific treatments for each specific type of factor deficiency that women with bleeding disorders could have and not every country has all the treatments available.

The EHC Women and Bleeding Disorders Committee is preparing a workplan on how to address the above-mentioned, and other, challenges.

Thank you to Tatjana, Naja and Ana for sharing their experiences and ideas!

World Haemophilia Day 2018: 'Principles and Partnerships'

Written by Raia Mihaylova, EHC Communications Officer

The evolving of haemophilia research has identified comprehensive care as the optimal approach to treating people with haemophilia. But only ten years ago, there were no haemophilia centres, no patient involvement or attention from governments on the issues faced by this part of the population. It was this landscape that set the scene for the establishment of the European Principles of Haemophilia Care, which became the standard for the provision of comprehensive haemophilia care in Europe as we know it today.

Professor Brian Colvin, lead author of the European Principles of Haemophilia Care, presented the landscape in which they were written ten years ago.

As 2018 marks ten years since their publication, the EHC and the European Association for Haemophilia and Allied Disorders (EAHAD) jointly marked World Haemophilia Day with an event that re-visited the fundamentals of the principles, as well as the partnerships that have driven their implementation forward. On April 19th, together with their lead author, Brian Colvin, the two organisations presented the history of the principles and the initiatives that have since arisen, forming a full circle in the advocacy for optimal comprehensive care in all European countries.

European Principles of Haemophilia Care

In 2005, attempts to start the conversation on establishing standards for haemophilia care were met with little action. It is at this time that Professor Peir Mannucio Mannuccio, Professor Ludlam and Dr Astermark decided to make further progress on uniting Europe in its approach to providing comprehensive treatment and care to the haemophilia population. At the time, the Eastern bloc had changed enormously, a number of countries in the East were getting ready for a more advanced haemophilia care and Romania and Bulgaria were preparing for accession to the European Union. Some European countries were producing their own guidance but there were no European Principles. The nature and quality of care in Europe was very varied, especially as the former Eastern European countries emerged (and indeed Russia has put much effort into haemophilia care). The Principles were partly designed to help emerging countries to persuade their governments, carers and patients of the need to support people with haemophilia, but without introducing unachievable goals. Bringing in all stakeholders, the idea was to cover the whole of comprehensive care, not just the treatment centre. After various meetings and discussions, the final version of the Principles covered organisation, governments, bureaucracy, funding, delivery and all the detail of what is required to look after somebody with haemophilia. The Principles grew out of the opinions of all the stakeholders who contributed to the paper.

Partnerships

Sustainable management of haemophilia care has always required active collaboration between all stakeholders. Not only does this approach provide for better treatment and care, but it is also a strength in addressing challenges, such as access to replacement therapy, patient empowerment and safe introduction to novel therapies.

With this in mind, the EHC and EAHAD have worked closely together on a number of initiatives, forming a partnership that has proven to be of value in improving treatment and care throughout the years. Through a Memorandum of Understanding (MoU), the two organisations have interacted on projects, such as the European Haemophilia Safety Surveillance (EUHASS), a pharmacovigilance program that monitors the safety of treatments for people with inherited bleeding disorders. Currently, both EHC and EAHAD are also in the process of signing an MoU with the European Association for the Study of the Liver (EASL) Foundation to eradicate hepatitis C in the haemophilia community by 2022.

In 2016, the EHC and EAHAD held their first joint meeting to discuss the challenges and needs of people with rare bleeding disorders and inhibitors. As a result, the European Principles of Inhibitor Management were established and have recently been accepted for publication in the *Orphanet Journal of Rare Diseases*. At the event, lead author and Chair of the EHC Medical Advisory Board, Dr Paul Giangrande, introduced the EHC-EAHAD collaboration in place that led to their creation.

Table 1: Ten European Principles of Inhibitor Management
1. Awareness of the incidence of inhibitors and risk factors across the life-span
2. Early recognition and accurate diagnosis
3. Optimal organization of care and communication between all stakeholders
4. Haemostatic treatment with bypassing agents in inhibitor patients
5. Inhibitor eradication by immune tolerance induction (ITI) therapy
6. Access to, and optimal preparation for, surgery and other invasive procedures
7. Provision of specialist nursing care
8. Provision of tailored physiotherapy care and monitoring
9. Access to psychosocial support
10. Involvement in research and innovation

Dr Paul Giangrande: We are really building on to the original European Principles of Haemophilia Care. It has been clear to us, within the EHC, that there are deficiencies in treatment of patients with an inhibitor around Europe. It is very useful that we have done these European surveys, which document, for instance, that patients with inhibitors are often denied surgery, they are not getting access to immune tolerance induction (ITI) because of cost and in some countries, they are not even getting by-passing therapy for acute bleeds. We felt that there is a deficiency and we had to focus on the patients with inhibitors to improve care. Together with our partners in EAHAD, we had a series of face-to-face meetings and we reviewed the literature. Over an 18- month period, we came up with these recommendations. I think what is good about these recommendations is, firstly, we have representatives from 13 European countries, we've got a truly multidisciplinary team who has produced these guidelines. We've got doctors, we've got people with haemophilia, we've got physiotherapists on board, we've got nurses, dental surgeons….

I think the input from the patient groups from the various countries has been absolutely pivotal in guiding us, not only in the establishment of the European Principles on Inhibitor Management, but also in the wider work of the European Inhibitor Network within the EHC.

RM: Now that they are accepted for publication, what does this mean?

I think once they are published, I see this as becoming a key advocacy tool. They will have a wide impact not just within the EU, but beyond that.

Initiatives arising from the European Principles of Haemophilia Care

"You can't get to the destination if you don't know where you're going!"

-Brian O'Mahony, EHC President, on the fundamental power of the European Principles of Haemophilia Care

EHC PARTNERS programme

To address urgent issues in the disparities of haemophilia care throughout Europe, in 2017 the EHC developed an innovative approach to create a sustainable procurement model for treatment for haemophilia A and haemophilia B in countries located both inside and outside of the European Union. The criteria and aims of the programme were based on the European Directorate for the Quality of Medicines and Healthcare (EDQM) recommendations on haemophilia care, which in turn were drafted with consideration of the European Principles of Haemophilia Care.

Declan Noone, EHC PARTERS programme consultant, shares how the principles and the EDQM recommendations were incorporated into the PARTNERS programme.

Declan Noone: The PARTNERS programme tries to incorporate all of the ten Principles in some form or another. The key two that drive it are Principle one and four. I think those two Principles, which have driven the establishment of three of the twelve EDQM recommendations, resulted in the concept of a centralised tender board with the involvement of patients and clinicians alongside the payers, the hospital contractors and everybody who has an important role in terms of provision of haemophilia care. Those are probably the two core Principles that have really been taken on board because everything beyond that is built out of them.

It is all connected. For example, we also have to consider the Principle of having national patient registries. If you don't have good data on who you are providing care for, it is very difficult to know how much factor concentrate you will need or have a proper tender in process. With a national registry, you can always predict how much you will need going forward.

Participants at the World Haemophilia Day event

Eventually, you want to get to the point where you are providing enough treatment for prophylaxis and patients needing surgery, specialist and emergency care, as well as for the management of inhibitors. Once you start layering these on top of each other and move them forward, this is where the key principle of PARTNERS ends up, being based on the EDQM recommendation of having four international units (IU) per capita of factor VIII treatment. The programme can often look like it is just a procurement programme but it's built around the EDQM recommendations, which are built around the European Principles of Haemophilia Care.

RM: What are some of the challenges that you have come across in the countries participating in PARTNERS?

DN: A combination of things. In some countries, it is the lack of a patient registry, in other countries it is the lack of the way products are compared against each other, lack of national treatment protocols. If you don't have a target to aim for, it is very difficult to know what you need. If you don't have the national patient registry and know how you want to treat patients through national treatment protocols then that leaves a deficit in terms of what we need and what we are currently purchasing. How do you bridge that gap?

Overall, the biggest challenge is that we are introducing a new system and people are not entirely sure how to incorporate it into the system already in place. In some countries, the system is ready; in others, there still needs to be movement from the Ministry of Health.

In the long-term future, what we would want to see is systems set up in all the individual countries to properly assess the real value of whatever treatment is chosen within that country and to improve the overall health of the entire population. You don't want to have patients in the capital cities getting better treatment than those in the regional hospitals, that is unfair to the entire patient population as a group. Hopefully, going forward we will see that the IU per capita for haemophilia treatment for the country is the same no matter where you are.

Since 2009, the EHC has carried out surveys that have monitored to what extent the European Principles of Haemophilia Care are implemented and reflect the reality throughout Europe. The results of these surveys have meaningfully contributed to the data that led to the establishment of the EDQM recommendations on haemophilia care. A country by country heat map that highlights the changes, improvements and areas that are still lacking behind is now live and can be accessed at https://www.ehc.eu/data-collection/.

Conclusions

Closing the event, speakers and participants discussed future challenges and the role the European Principles of Haemophilia Care will have in addressing them. Though the haemophilia landscape is changing with the emergence of novel therapies, the ideal of looking after people with haemophilia in a comprehensive way cannot change. Looking forward, the European Principles of Haemophilia Care will remain relevant, with quite some work left to do in terms of establishing principles for von Willebrand Disease and other rare bleeding disorders.

Pictured from left to right: Dr Paul Giangrande, Prof Brian Colvin, Prof Cedric Hermans, Amanda Bok and Declan Noone

Bike ride "Together": **One Initiative** throughout **Four Cities** raising **Haemophilia Awareness**

Interview with Maria Nedevska, organiser of the information campaign around the bike ride and responsible for the public relations of the Bulgarian Haemophilia Association, EHC Bulgarian NMO; Interview taken by Raia Mihaylova, EHC Communications Officer

With the approach of World Haemophilia Day on April 17th, various awareness campaigns are sweeping cities around the world in support of people with haemophilia. To mark the day, the Bulgarian Haemophilia Association is organising a simultaneously social and sport bike ride initiative under the slogan "Sharing is Power." Held for the third year in a row, the Association aims to shed light to the challenges with access to haemophilia treatment in the country. Through the slogan, they call on the public sector and health care institutions to better collaborate with the non-governmental organisations that work to improve the living conditions of children, young people and adults, or in this case - people with haemophilia. Maria Nedevska, organiser of the information campaign around the bike ride, shares behind-the-scenes details of what it takes to organise an awareness campaign.

This year, the slogan of the bike ride initiative is "Sharing is Power." What is one piece of information that you think is important to share, what needs to be known?

What needs to be known and shared is that people with haemophilia can absolutely fully participate in society, as long as they have good access to treatment. They should also not live with stigma. For example, in kindergartens across Bulgaria, and not only in Bulgaria, there is an attitude of parents who discourage their own children to play with kids with haemophilia with words such as "don't play with him, you might hurt him" and so on.

There are a lot of other barriers that exist too. Unfortunately, due to lack of prophylaxis treatment and other past circumstances, many adults with haemophilia have limited mobility. Largely for that reason, they develop a psychological barrier, and not only psychological. They have limited

opportunities for professional development, there are many professions that won't adapt to their needs. So really, those are our main aims: not only do we want to make the government institutions in Bulgaria more involved and responsible, but the more information we share, the more people are informed, the more tolerant they become. That is why the bike ride initiative is named "Together" – it emphasises the principle that, with the help of modern treatment and social support, people with haemophilia can participate actively in a society.

This is the third year in a row that the initiative is being held. Each year it has grown bigger, how do you go about organising such an awareness event?

Last year was the first time I helped with the organisation. I work in public relations but this kind of a social initiative was a debut for me. It was something massive because we were doing it in the cities of Sofia, Plovdiv and Varna at the same time. My idea was to have a large national media campaign and to also, of course, use social media to publicise it. Another idea I had was to unite with the non-governmental sector because in Bulgaria, it is quite developed. There is a lot of noise and attention around large non-governmental organisations, such as "The National Network for Children." Last year, they shared our event on their Facebook page; this year, we have already met and decided on a much more adequate way to collaborate on this campaign. For example, now we are doing explanatory infographics on early diagnosis, which they will disseminate to their large parent network.

Bike ride "Together" 2017

Last year, I was also really happy to see that in the final stage of our campaign leading up to the bike ride initiative, we got a lot of national coverage. Now, we have even stronger media support and we started planning everything much earlier.

This year, the event is carried out under the patronage of the Embassy of Denmark and the Bulgarian Ministry of Health. How did you manage to get them involved?

While meeting with certain organisations, we would discuss how we can spread the information wider and a lot of the ideas were born that way – in action. The Embassy of Denmark has a tradition of supporting and organising initiatives in the areas of tolerance, health, community and bike riding as a city sport. We were put in contact with them and they wholeheartedly joined. The ambassador Søren Jacobsen is ready to

join our media campaign and support everything around it. We're thankful to them and the Bulgarian Ministry of Health, as well as to the local municipalities.

"It is important to me to take part in the bike ride because this way, more people will understand about our condition and that it is not something that is contagious or dangerous to them. We are not any different. When I participated last year, I was so excited and thrilled to see all those people who took from their time to come for one day and support us."

Victor Velinov, participant in the bike ride

The bike ride initiative will take place on April 21th simultaneously in Bulgaria's four biggest cities – Sofia, Plovdiv, Varna and Burgas.

Upcoming 2018 EHC events

June 7-10	**Leadership Conference** Brussels, Belgium Open to NMOs only
June 19	**Round Table on Women and Bleeding Disorders** Brussels, Belgium Open to select participants
September 14-16	**Tenders and Procurement Workshop** Location to be confirmed Open to NMOs only
October 5-7	**2018 EHC Conference** Brussels, Belgium Open to all
November 20	**Round Table - Switching from Standard Therapies: Where do Novel Therapies Fit In** Brussels, Belgium Open to select participants
November 23-25	**New Technologies in Haemophilia Workshop** Sofia, Bulgaria Open to NMOs only
December 6-9	**European Inhibitor Summit** Barretstown, Ireland Open to NMOs only

Other events 2018

May 10-12

European Conference on Rare Diseases and Orphan Products
Vienna, Austria
More information at https://www.rare-diseases.eu/

May 20-24

2018 World Federation of Hemophilia World Congress
Glasgow, Scotland
More information at https://www.wfh.org/congress/en/home

June 14-17

2018 European Hematology Association Annual Congress
Stockholm, Sweden
More information at http://eha-2018.org/index.html

July 18-21

Annual Scientific and Standardization Committee Meeting of the International Society on Thrombosis and Haemostasis (ISTH)
Dublin, Ireland
More information at http://www.ssc2018.org/